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(71) Applicant *(for all designated States except US)*: **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **DUNNE, Michael, William** [US/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).

(74) Agents: **LUMB, J., Trevor** et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

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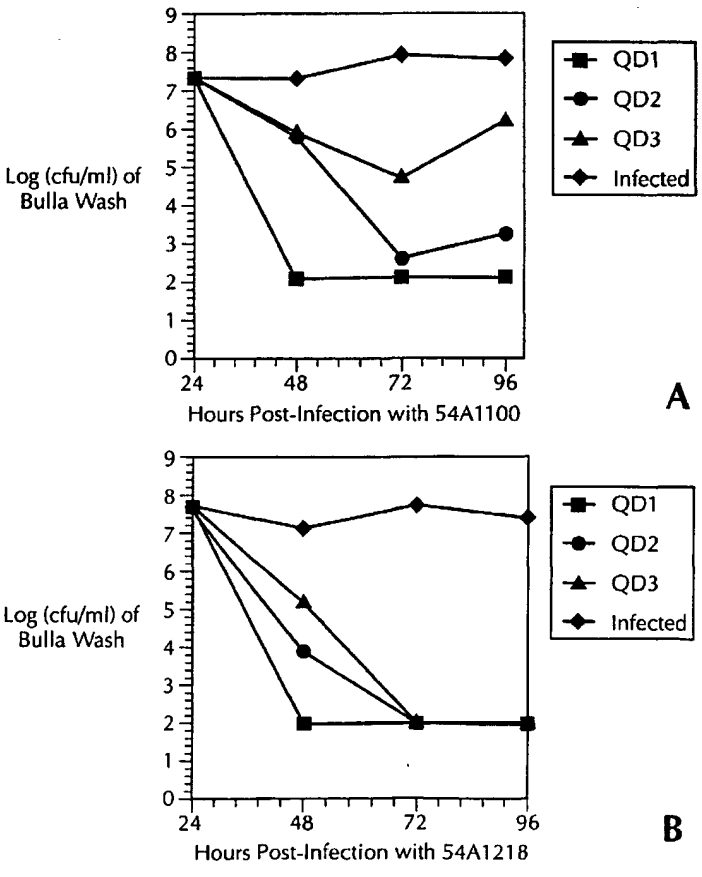
(54) Title: SINGLE DOSE AZITHROMYCIN



(57) Abstract: The present invention relates to a method of treating respiratory infections in humans by administering a single dose of azithromycin.

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SINGLE DOSE AZITHROMYCIN

This application is a continuation-in-part of US Patent Application 60/313,867, filed August 21, 2001, which is hereby incorporated by reference herein in its entirety.

Field of the Invention

The present invention relates to a method of treating respiratory infection by administering a single dosage of azithromycin.

Background of the Invention

Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antimicrobial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, US Pat. No. 4,474,768 and Kobrehel et al., US Pat. No. 4,517,359. These patents disclose that azithromycin and certain derivatives thereof possess antibacterial properties and are accordingly useful as antibiotics. Azithromycin may be made, formulated and administered according to procedures described in the following US patents, which are all incorporated herein in their entirety by reference: US Pat. Nos. 6,268,489; 4,963,531; 5,633,006; 5,686,587; 5,605,889; 6,068,859; 4,328,334; and 5,498,699.

Azithromycin is administered for the treatment of infections, particularly respiratory infections, and more particularly respiratory infections of the bronchial tract, lungs, and sinus. Frequently, azithromycin is prescribed for acute otitis media. Acute otitis media is an inflammation of the area behind the eardrum (tympanic membrane) in the chamber called the middle ear. Acute otitis media is an infection that produces pus, fluid, and inflammation within the middle ear.

Acute otitis media may be caused by a variety of pathogens, such as *M. catarrhalis*, *S. pneumoniae*, and *H. influenzae*. Acute otitis media is particularly common in infants and children. Azithromycin has been prescribed for the treatment of acute otitis media with a 30 mg/kg body weight total treatment dose given as a five day regimen in the US and as a three day regimen in Europe. The multiple dosages prescribed to completely cure the infection have caused compliance problems, particularly in pediatric patients. Even in the adult population, compliance with multiple dosaging regimens is not complete because of forgetfulness and other reasons. A method of treating and curing infection, particularly a microbial infection such as acute otitis media, by administering a single dose of azithromycin would significantly shorten courses of therapy and be of a great advantage to patient compliance.

A continual problem with antibiotic therapy is the emergence of resistant microbial strains. A method of treating microbial infections with a reduced risk of developing treatment-resistant strains is desirable. It is believed that a single dose azithromycin treatment provides such as reduced risk. The inflammatory cells provide a mode of transport of azithromycin to the infection site and provide a reservoir for azithromycin at the infection site. As a result, azithromycin is characterized by high and sustained concentrations in a wide range of tissues, and a particularly increased concentration at sites of infection. It is believed that a single dose therapy with azithromycin, by providing a higher initial concentration at the infection site, may help prevent less susceptible sub-populations of the pathogens initially present from becoming established. Also, a single-dose regimen will result in greater patient compliance, which should contribute to reduced emergence of less susceptible strains.

Single dose administration of azithromycin for the treatment of non-gonococcal urethritis and cervicitis due to *C. trachomatis* has been prescribed and is a therapy approved by the US Food and Drug Administration. Single dose treatment of respiratory infections in humans with azithromycin has been tested. For example, Stan Block et al. reported on single dose azithromycin (30 mg/kg) in acute otitis media in infants and children six months to twelve years of age. S. Block *et al.*, "Single-Dose Azithromycin (30 mg/kg) in Acute Otitis Media", Arguedas reported on single-dose therapy in otitis media using azithromycin in infants and children. Arguedas, A., "Single-dose therapy in otitis media", Poster Presentation at 9th European Congress of Clinical Microbiology and Infectious Diseases, Berlin, Germany, March 21-24, 1999, *Clin. Microbiol. Infect.* 1999:5 (Supp. 3 March):28 (Abstr). A single oral dose of 2g azithromycin was administered to healthy male subjects in tests of gastrointestinal side effects reported in US Pat. No. 6,068,859. Despite these reports, there exists a need for a method of treating respiratory infections such as acute otitis media with a single dose of azithromycin such that the infection is cured.

Summary of the Invention

The present invention fulfills these needs by providing a method of treating a respiratory infection in a human comprising administering to a human in need thereof a single dose of azithromycin wherein the dose is about 35mg/kg body weight or greater. In another embodiment, the invention is directed to a method of treating a respiratory infection in a human comprising administering to a human in need thereof a single dose of azithromycin wherein the dose is within the range of about 0.7 to 3.5 g. A further embodiment is directed to a method of treating a respiratory infection caused by *S. pneumoniae* isolates containing a

mef A gene in a human comprising administering to a human in need thereof a single dose of azithromycin wherein the dose is about 35mg/kg body weight or greater.

Brief Description of the Drawings

Figures 1a and 1b show the eradication of *H. influenzae* in a gerbil model of middle ear infection.

Detailed Discussion

The invention provides a method of treating respiratory infections in a human in need thereof by administering a single dose of azithromycin. The human patient may be an adult sixteen years of age or older, a child under sixteen years of age, or a young child twelve years of age or younger. By "single dose" is meant a dosage that is administered only once over a 28-day period. The dosage may be administered in a single dosage form, such as one capsule or tablet, or may be divided, e.g. constituted by more than one dosage form, such as by multiple capsules or tablets that are taken at or about the same time. Any type of dosage form may be used, such as capsule, tablet, liquid suspension for oral administration, or liquid for intravenous administration.

The "single dose" of the invention is formulated for immediate release and is not formulated for controlled, sustained or delayed release. For example, an orally administered azithromycin single dose administered according to the present invention is preferably in a form such that it releases azithromycin to the human gastrointestinal tract at a rate such that the total amount of azithromycin released therein is more than 4 mg of azithromycin per kg of patient weight in the first fifteen minutes after ingestion and more preferably is more than 40 mg of azithromycin per kg of weight in the first six hours after ingestion.

Azithromycin can be employed in its pharmaceutically acceptable salts and also in anhydrous as well as hydrated forms, such as the di- and mono-hydrates. All such forms are within the scope of this invention. The azithromycin employed is preferably the dihydrate, which is disclosed in published European Patent Application 0 298 650 A2.

Under the inventive methods, respiratory infections in humans are treated by administering azithromycin in a single dose of about 35mg/kg body weight or greater. Preferably, the single dose is between about 35mg/kg and 60mg/kg body weight, and yet more preferably between about 40mg/kg and 50mg/kg body weight. In other embodiments, the single dose is between about 35mg/kg and 40mg/kg, between about 40mg/kg and 45mg/kg, between about 45mg/kg and 50mg/kg, or between about 50mg/kg and 60mg/kg. In another embodiment, the single dose of azithromycin is administered at a dose within the

range of about 0.7 to 3.5 g, preferably a dose within the range of about 0.7 to 1.5 g or about 1.5 to 3.1g. Yet more preferably the dose is within the range of about 1.5 to 1.9 g, and more preferably within the range of about 2.1 to 3.1 g. In other embodiments, the single dose is selected from the group consisting of 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0 and 3.1g.

The methods of the invention may be used to treat infections caused or mediated by different pathogens. Preferably, the pathogen is selected from *S. aureaus*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. pyrogenes*, and more preferably is selected from *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. The invention preferably is directed to treating a respiratory infection such as acute otitis media caused or mediated by one of these specified pathogens.

Examples

1.0 Single Dose Azithromycin Pediatric Test

A trial was preformed using a single 30-mg/kg dose of azithromycin in the treatment of otitis media in pediatric patients undergoing diagnostic tympanocentesis. Children six months to twelve years were enrolled. Of the patients who had a pathogen identified at baseline by culture, 81% were cured by the single dose therapy. Cure was defined by a clinical assessment at day 24-28 showing complete resolution of all signs and symptoms of acute otitis media. Cure rates were highest for *M. catarrhalis* (10/10; 100%) followed by *S. pneumoniae* (67/76; 88%) and *H. influenzae* (28/44; 64%).

Twelve children were found to have an infection with an isolate of *S. pneumoniae* resistant to macrolides. Five children had an infection of an isolate that contained the erm B gene. Only two of these five patients were cured at day 28. Seven children had an infection of an isolate that contained the mef A gene. Six of these seven patients were cured at day 28. The patient who failed was resolving the disease in the ear from which the baseline isolate was obtained but had a different *S. pneumoniae* isolate recovered on day 4 from the opposite ear. The high efficacy in the patients whose *S. pneumoniae* isolate were found to contain the mef A gene was unexpected and surprising.

2.0 Single Dose Azithromycin Animal Tests

Laboratory experiments with azithromycin suggest that it is the total amount of drug rather than the interval of the drug dosing regimen that determines the concentration at the infection site and results in efficacy. Acute murine models challenged with *S. pneumoniae*, *H. influenzae*, *E. faecalis* or *S. pyrogenes* showed that azithromycin was superior in efficacy when given as a single oral dose as determined by PD_{50} measurements (*see* Table 1).

Table 1. The Effect of Dose Regimen on Efficacy of Azithromycin in Murine Models.

Pathogen	MIC (μg/ml)	Dosing Regimen	Oral PD50 (mg/kg/day)
H. influenzae		3 days	181.6 (180.1-183.1)
		2 days	49.9 (41.5-58.5)
		1 day	25.3 (14.3-36.2)
S. pyogenes	0.06	3 days	3.8 (3.8-3.9)
		2 days	2.5 (1.8-3.3)
		1 day	1.0 (0.6-1.4)
E. faecalis		3 days	59.3 (27.5-91.2)
		2 days	42.7 (42.2-43.2)
		1 day	14.8 (10.2-19.5)
S. pneumoniae	0.06	3 days	49.4 (28.1-70.8)
		2 days	27.6 (22.8-32.4)
		1 day	20.4 (16.4-24.3)

The improvement in the PD_{50} for treatment of *H. influenzae* was especially noteworthy. In a gerbil model of middle ear infection, two different strains of *H. influenzae* 54A1100 and 54A1218 were shown to be as efficaciously treated with azithromycin administered as a single dose as the same total dose given over two or three days (*see* Table 2). In these experiments, colony-forming units (CFU) are assessed from the bulla wash of five gerbils per time point. The ED50 values reflect the dose in which the CFU recoverable from the bulla wash is 50% of the non-treated animals.

Table 2. The Effect of Dose Regimen on Efficacy of Azithromycin in the Gerbil Middle Ear Infection Model.

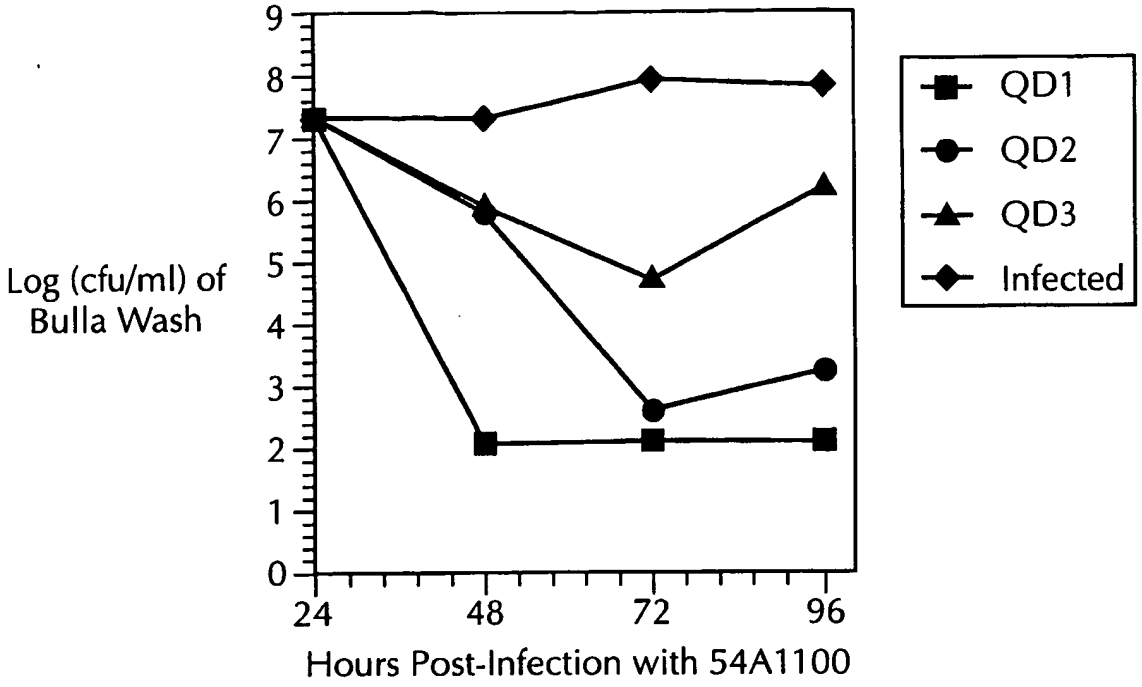
Pathogen	MIC (μg/ml)	Dosing Regimen	ED50 (mg/kg/total)
H. influenzae	1	3 days	162.9 (140-185.9)
		2 days	138.1 (118.7-157.6)
		1 day	138.1 (118.7-157.6)

The in vivo kill kinetics demonstrated that the one-day dosing therapeutic regimen resulted in the most rapid eradication of the pathogens (Figure 1) and, in the case of 54A1100, was the only dosing regimen that leads to complete clearance. Thus, a single dose therapy has advantages over a more prolonged course of therapy.

CLAIMS

1. A method of treating a respiratory infection in a human comprising administering to a human in need thereof a single dose of azithromycin wherein the dose is about 35mg/kg body weight or greater.
2. The method of claim 1 wherein the dose is between about 35mg/kg and 60mg/kg body weight.
3. The method of claim 2 wherein the dose is between about 40mg/kg and 50mg/kg body weight.
4. The method of claim 2 wherein the human is an adult sixteen years of age or older.
5. The method of claim 2 wherein the respiratory infection is acute otitis media.
6. A method of treating a respiratory infection in a human comprising administering to a human in need thereof a single dose of azithromycin wherein the dose is within the range of about 0.7 to 3.5 g.
7. The method of claim 6 wherein the respiratory infection is acute otitis media.
8. The method of claim 6 wherein the dose is within the range of about 0.7 to 1.5 g.
9. The method of claim 6 wherein the dose is within the range of about 1.5 to 3.1 g.
10. The method of claim 9 wherein the dose is within the range of about 1.5 to 1.9 g.
11. The method of claim 9 wherein the dose is within the range of about 2.1 to 3.1 g.
12. The method of claim 9 wherein the human is an adult sixteen years of age or older.
13. A method of treating a respiratory infection caused by *S. pneumoniae* isolates containing a mef A gene in a human comprising administering to a human in need thereof a single dose of azithromycin wherein the dose is about 35 mg/kg body weight or greater.
14. The method of claim 13 wherein the dose is between about 35mg/kg and 60mg/kg body weight.
15. The method of claim 13 wherein the dose is between about 40mg/kg and 50mg/kg body weight.

FIG. 1A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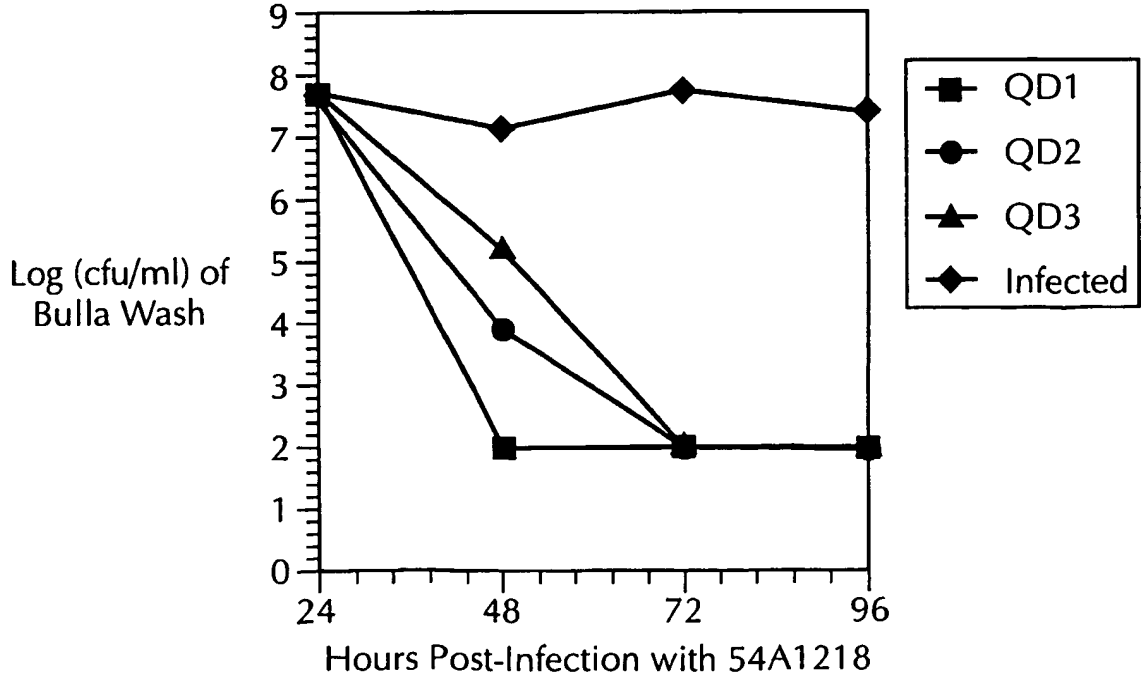
1
2
3
4
5
6
7
8
9
24
48
72
96
Hours Post-Infection with 54A1100
QD1
QD2
QD3
Infected

FIG. 1B


Log (cfu/ml) of Bulla Wash
0
1
2
3
4
5
6
7
8
9
24
48
72
96
Hours Post-Infection with 54A1218
QD1
QD2
QD3
Infected

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(71) Applicant *(for all designated States except US)*: **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

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(74) Agents: **LUMB, J., Trevor** et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

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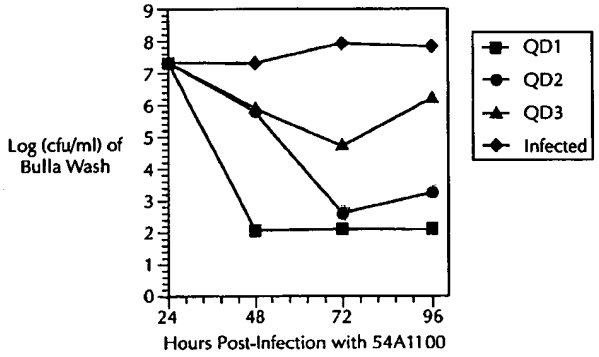
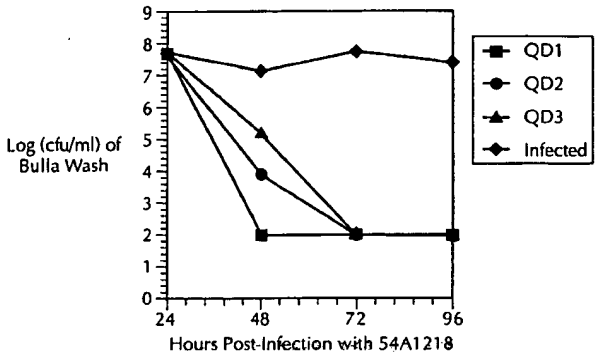
[Continued on next page]

(54) Title: SINGLE DOSE AZITHROMYCIN FOR TREATING RESPIRATORY INFECTIONS

(57) Abstract: The present invention relates to a method of treating respiratory infections in humans by administering a single dose of azithromycin.





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INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7052 A61P11/00 A61P31/04 A61P27/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
MEDLINE, BIOSIS, EMBASE, EPO-Internal, WPI Data, PAJ, CHEM ABS Data, PHARMAPROJECTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHÖNWALD S ET AL: "Azithromycin: single 1.5 g dose in the treatment of patients with atypical pneumonia syndrome--a randomized study." INFECTION. GERMANY 1999 MAY-JUN, vol. 27, no. 3, May 1999 (1999-05), pages 198-202, XP008018295 ISSN: 0300-8126 the whole document --- -/--	1-4,6, 8-10,12

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 June 2003	02/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AMSDEN G W ET AL: "Serum and WBC pharmacokinetics of 1500 mg of azithromycin when given either as a single dose or over a 3 day period in healthy volunteers." THE JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY. ENGLAND JAN 2001, vol. 47, no. 1, January 2001 (2001-01), pages 61-66, XP001159703 ISSN: 0305-7453	1-4,6, 8-10,12
Y	see the whole document, especially page 61, page 62 left column paragraphs 1-2, page 63 right column first paragraph.	5,7
Y	BLOCK STAN L ET AL: "Single dose azithromycin (30 mg/kg) in acute otitis media." CLINICAL INFECTIOUS DISEASES, vol. 31, no. 1, July 2000 (2000-07), page 243 XP008018309 2000 Annual Meeting of the Infectious Diseases Society of America;New Orleans, Louisiana, USA; September 07-10, 2000 ISSN: 1058-4838 cited in the application the whole document	1-15
Y	MÜLLER O: "Comparison of azithromycin versus clarithromycin in the treatment of patients with upper respiratory tract infections." THE JOURNAL OF ANTIMICROBIAL CHEMOTHERAPY. ENGLAND JUN 1993, vol. 31 Suppl E, June 1993 (1993-06), pages 137-146, XP008018300 ISSN: 0305-7453 the whole document	1-15
Y	NIGHTINGALE C H ET AL: "Comparative bactericidal activity of clarithromycin, azithromycin, and cefuroxime against Streptococcus pneumoniae" JOURNAL OF INFECTIOUS DISEASE PHARMACOTHERAPY 1999 UNITED STATES, vol. 4, no. 1, 1999, pages 17-24, XP008018297 ISSN: 1068-7777 the whole document	1-15

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	AOKI N: "Pharmacokinetics of azithromycin and its clinical results" JAPANESE JOURNAL OF CHEMOTHERAPY 1995 JAPAN, vol. 43, no. SUPPL. 6, 1995, pages 234-238, XP008018296 ISSN: 1340-7007 abstract; tables 4,6 ---	1-4
Y	MORRIS D L ET AL: "High and prolonged pulmonary tissue concentrations of azithromycin following a single oral dose." EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY & INFECTIOUS DISEASES: OFFICIAL PUBLICATION OF THE EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY. GERMANY OCT 1991, vol. 10, no. 10, October 1991 (1991-10), pages 859-861, XP008018299 ISSN: 0934-9723 the whole document ---	1-4
Y	KLEPSER M ET AL: "Efficacy of clarithromycin (CL) and azithromycin (AZ) against Streptococcus pneumoniae (SPN) with various macrolide resistance mechanisms in a neutropenic murine respiratory infection model." INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS, vol. 17, no. Supplement 1, June 2001 (2001-06), page S157 XP002244592 22nd International Congress of Chemotherapy;Amsterdam, Netherlands; June 30-July 03, 2001 ISSN: 0924-8579 abstract ---	13-15
A	BERGOGNE-BEREZIN EUGENIE: "Azithromycin: Tissue pharmacokinetic data." PATHOLOGIE BIOLOGIE, vol. 43, no. 6, 1995, pages 498-504, XP008018308 ISSN: 0369-8114 the whole document --- -/--	1-15

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,Y	JORGENSEN DANIEL M ET AL: "Single dose azithromycin is safe and effective in the treatment of acute otitis media." PEDIATRIC RESEARCH, vol. 51, no. 4 Part 2, April 2002 (2002-04), page 284A XP008018310 Annual Meeting of the Pediatric Societies';Baltimore, MD, USA; May 04-07, 2002, April, 2002 ISSN: 0031-3998 abstract 1654 ---	1-15
P,Y	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2002 GIRARD D ET AL: "Accelerated dosing of azithromcyin in preclinical infection models." Database accession no. PREV200200584685 XP002244593 abstract & ABSTRACTS OF THE GENERAL MEETING OF THE AMERICAN SOCIETY FOR, vol. 102, 2002, page 11 102nd General Meeting of the American Society for Microbiology;Salt Lake City, UT, USA; May 19-23, 2002, http://www.asmusa.org/mtgsrc/generalmeetin g.htm 2002 ISSN: 1060-2011 -----	1-15

INTERNATIONAL SEARCH REPORT

Internal application No.
PCT/IB 02/03076

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.